General

Guideline Title

Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update.

Bibliographic Source(s)

World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva (Switzerland): World Health Organization; 2011. 44 p. [52 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization (WHO); 2008. 247 p.

It is expected that the World Health Organization's Stop Tuberculosis (TB) Department, in collaboration with its partners, will review and update these guidelines about four years after their publication or earlier if new evidence, regimens or diagnostic tests become available.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 12, 2016 – Fluoroquinolone Antibacterial Drugs : The U.S. Food and Drug Administration (FDA) is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

Recommendations

Major Recommendations

The definitions for the quality of the evidence (high, moderate, low, very low) and the strength of the recommendations (strong, conditional) are

provided at the end of the "Major Recommendations."

Note from the World Health Organization (WHO): The recommendations in these guidelines are to be read along with the accompanying remarks on available evidence, which are relevant to their proper interpretation and implementation.

Rapid Drug Susceptibility Testing for Early Start of Appropriate Treatment

Recommendation

Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of tuberculosis (TB), subject to available resources (conditional recommendation, +000/very low quality evidence).

Evidence

The evidence used to determine the optimal timing of drug susceptibility testing (DST) and the method of testing to be used relied on simulations from modelling work. There are inherent limitations when using models, which are linked to the underlying assumptions. Sensitivity analyses, however, showed fairly consistent results when epidemiological conditions and costs were varied.

For the purposes of the recommendation, the group considered a rapid test as one providing a diagnosis of resistance to isoniazid and rifampicin or rifampicin alone within two days of specimen testing. Only molecular tests can detect resistance so fast, of which two technologies – line probe assay and Xpert MTB/RIF – are currently recommended for use by the WHO. Conventional DST of cultured mycobacteria typically provides results within 1–3 months.

Outcomes of interest were reduced mortality, increased likelihood of cure, decreased development of additional resistance, and reduced likelihood of failure and relapse, expressed as the cost per disability-adjusted life year (DALY) averted. The model did not take into consideration ongoing transmission that may occur if diagnosis of resistance is delayed.

Monitoring the Response to Multidrug Resistant TB (MDR-TB) Treatment

Recommendation

The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDR-TB during treatment (conditional recommendation, +000/very low quality evidence).

Evidence

The evidence used to assess how best to monitor treatment in MDR-TB patients using sputum smear microscopy and culture in settings with reliable direct microscopy was based on data pooled from 10 published observational studies. Monthly monitoring by culture was used as the reference in all the analyses. Random-effects Cox proportional hazards models were used to estimate the hazard ratio of failure, comparing monthly culture to alternative monitoring strategies.

Composition of Second-Line Anti-Tuberculosis Regimens

Recommendations

1. In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, +000/very low quality evidence).
2. In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, +000/very low quality evidence).
3. In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, +000/very low quality evidence).
4. In the treatment of patients with MDR-TB, four second-line antituberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase* (conditional recommendation, +000/very low quality evidence).
5. In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, +000/very low quality evidence).

*The intensive phase is the initial part of a course of treatment during which a parenteral (injectable) agent is used.

Evidence

The evidence used to address the questions on which drugs to include (with or without information on their DST patterns) and the number of drugs

to be used in regimens for MDR-TB patients was based on studies published in three major systematic reviews. All three reviews searched EMBASE and MEDLINE databases as well as the Cochrane Library and the ISI Web of Science. Studies published before 1970 and those including only extensively drug-resistant tuberculosis (XDR-TB) cases were excluded. The reviewers then pooled individual patient data from studies which had featured in the systematic reviews for a meta-analysis.

The meta-analysis included 32 studies with more than 9000 treatment episodes for which the authors could be contacted and were willing to share their data. Patients with XDR-TB (N=410) were excluded, as their treatment regimens were considered not to be comparable with those of other MDR-TB patients. Cohorts included had to have had at least 25 subjects treated for MDR-TB, and one or more of the treatment outcomes meeting the standard definitions. Missing values for age, sex, past TB, extent of disease, human immunodeficiency virus (HIV) infection and DST were imputed (>50% of cohort members having an observed value for these variables), but not those for treatment modality or outcome. None of the cohorts was part of randomized controlled trials and thus the quality of evidence was judged to be low or very low. While the odds ratios in the analysis were adjusted for age, sex, HIV-serostatus, past TB treatment, past MDR-TB treatment and extent of disease, there remains a risk of substantial bias (certain drugs may have only been used for sicker patients). Other limitations included incomplete ascertainment of relapse, the under-representation of certain geographical regions, and missing data for some of the variables examined.

Findings from this analysis may not necessarily be generalizable to all populations in settings with high or low prevalences of drug resistance or different levels of resources. Nonetheless, the results of this analysis represented the best available evidence to date for the group to make recommendations on the composition of treatment regimens.

Table: Changes to the Recommendations on Regimen Composition Between the 2008 and 2011 Updates of the Guidelines

2008 Emergency Update	2011 Update
Include at least four anti-tuberculosis drugs with either certain, or almost certain, effectiveness during the intensive phase of treatment.	Include at least four second-line anti-tuberculosis drugs likely to be effective as well as pyrazinamide during the intensive phase of treatment.
Consider adding more drugs in patients with extensive disease or uncertain effectiveness.	No evidence found to support the use of more than four second-line anti-tuberculosis drugs in patients with extensive disease. Increasing the number of second-line drugs in a regimen is permissible if the effectiveness of some of the drugs is uncertain.
The regimen should include pyrazinamide and/or ethambutol, one fluoroquinolone, one parenteral agent and second-line oral bacteriostatic anti-tuberculosis drugs (no preference of oral bacteriostatic second-line anti-tuberculosis drug was made).	The regimen should include pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and cycloserine, or else PAS if cycloserine cannot be used.
Ethambutol may be considered effective and included in the regimen if DST shows susceptibility.	Ethambutol may be used but is not included among the drugs making up the standard regimen.
Treatment with Group 5 drugs* is recommended only if additional drugs are needed to bring the total to four.	Group 5 drugs* may be used but are not included among the drugs making up the standard regimen.

PAS=p-aminosalicylic acid

*Group 5 drugs include clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, clarithromycin, imipenem

Duration of Second-Line Anti-Tuberculosis Regimens

Recommendations

1. In the treatment of patients with MDR-TB, an intensive phase of at least 8 months' duration is recommended (conditional recommendation, +000/very low quality evidence).
2. In the treatment of patients with MDR-TB, a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment (conditional recommendation, +000/very low quality evidence).

Evidence

The evidence used to derive recommendations on the duration of treatment was based on an analysis of the same individual patient data collected

and described in the section "Composition of Second-Line Anti-Tuberculosis Regimens" above. All data were from observational studies, and the quality of evidence was classified as very low. Attempts to control for selection bias and confounding in this review are unlikely to have adjusted for all important factors, and patients who receive longer therapy may be those who are more sick. Patients with XDR-TB were also excluded from the analysis. The findings may not be generalizable to all populations in settings with high or low prevalence of drug resistance or with different levels of resources.

Use of Antiretrovirals in Patients on Second-Line Anti-tuberculosis Regimens

Recommendation

Antiretroviral therapy is recommended for all patients with HIV infection and drug-resistant TB requiring second-line anti-tuberculosis drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment (strong recommendation, +000/very low quality evidence).

Evidence

Evidence was reviewed from 10 studies to assess patient treatment outcomes when antiretroviral therapy (ART) and second-line anti-tuberculosis drugs were used together. None of the data were from randomized controlled trials. Individual patient data were available for 217 drug-resistant TB patients in total, of whom 127 received ART. The level of evidence in individual observational studies varied from low to very low quality.

Models of Care for Managing MDR-TB

Recommendation

Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization (conditional recommendation, +000/very low quality evidence).

Evidence

Outcomes from models of MDR-TB care based mainly on clinic-based ambulatory treatment were compared with those using mainly hospital-based inpatient treatment. The data used came from published and unpublished cost-effectiveness studies in four countries (Estonia, Peru, the Philippines and the Russian Federation [Tomsk oblast]). The design of these observational studies did not allow direct comparison of effects between models of care. Given that none of the studies were randomized controlled trials the evidence was considered very low. Cost-effectiveness was modelled for all possible WHO Member States in a probabilistic analysis of the data from the four countries.

Definitions:

Assessment of the Strength of the Recommendation

Strength	Definition
Strong	The Guideline Development Group is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Conditional	The Guideline Development Group concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects.

Quality of the Evidence

Quality of Evidence	Definition
High (++++)	Further research is very unlikely to change confidence in the estimate of effect.
Moderate (+++0)	Further research is likely to have an important impact on confidence in the effect and may change the estimate.
Low (++00)	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Quality of Evidence	Very low (+000) Definition Any estimate of effect is very uncertain.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Drug-resistant tuberculosis (DR-TB), including:

- Multidrug-resistant tuberculosis (MDR-TB)
- Extensively drug-resistant TB (XDR-TB)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Infectious Diseases

Pharmacology

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Health Care Providers

Health Plans

Hospitals

Managed Care Organizations

Nurses

Pharmacists

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

To provide a tool for use by public health professionals in response to the sixty-second World Health Assembly's call for Member States to develop a comprehensive framework for the management and care of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB)

The recommendations aim to:

- Address the most topical questions in MDR-TB control requiring guidance for which the best available evidence has been summarized through appropriate review of data
- Provide a reference for countries developing national guidelines and policies to scale up detection and treatment of MDR-TB as an integral part of their national programmes

Target Population

Patients with suspected or confirmed drug-resistant tuberculosis

Interventions and Practices Considered

Diagnosis

Rapid drug susceptibility testing (DST)

Treatment/Management

1. Monitoring treatment response (sputum smear microscopy, sputum culture)
2. Second-line treatment regimens
3. Duration of second-line therapy
4. Combination antiretroviral and anti-tuberculosis therapy
5. Ambulatory care model

Major Outcomes Considered

- Treatment failure rate
- Time to initiation of appropriate treatment
- Acquisition or amplification of drug resistance rate
- Death from tuberculosis (TB)
- Relapse rate
- Default or treatment interruption due to non-adherence
- Population coverage or access to appropriate treatment of drug-resistant TB
- Smear or culture conversion during treatment
- Accelerated detection of drug resistance
- Avoidance of unnecessary multidrug resistant (MDR)-TB treatment
- Population coverage or access to diagnosis of drug-resistant TB

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The evidence review teams assessed the evidence for the questions (see the "Description of the Methods Used to Analyze the Evidence" field) and their outcomes through a series of systematic literature reviews following an approved methodology that was documented (see Annex 1 in the original guideline document [see the "Availability of Companion Documents" field]). Titles, abstracts and full text of potentially relevant literature were screened using key subject words and text words. The search was not limited by study type or time period. Authors in the field and members of the Guideline Development Group were contacted to identify missing studies or studies in progress. Case-based data were collected from authors of published studies to analyse the effects relating to the questions dealing with bacteriology and treatment regimen (see questions 2–6 in the "Description of the Methods Used to Analyze the Evidence" field).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence	Definition
High (++++)	Further research is very unlikely to change confidence in the estimate of effect.
Moderate (+++0)	Further research is likely to have an important impact on confidence in the effect and may change the estimate.
Low (++00)	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low (+000)	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis of Summarized Patient Data

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The seven priority questions identified by the Guideline Development Group, worded in the PICO (Population, Intervention, Comparator, Outcome) or similar format were:

1. At what prevalence of multidrug-resistant tuberculosis (MDR-TB) in any group of tuberculosis (TB) patients is rapid drug-susceptibility testing warranted to detect resistance to rifampicin and isoniazid or rifampicin alone on all patients in the group at the time of TB diagnosis, in

order to prescribe appropriate treatment at the outset? *The evidence used to determine the optimal timing of drug sensitivity testing (DST) and the method of testing to be used relied on simulations from modelling work.*
2. Among patients with MDR-TB receiving appropriate treatment in settings with reliable direct microscopy, is monitoring using sputum smear microscopy alone rather than sputum smear and culture, more or less likely to lead to the outcomes listed in Table 2 of the original guideline document?
3. When designing regimens for patients with MDR-TB, is the inclusion of specific drugs (with or without documented susceptibility) more or less likely to lead to the outcomes listed in Table 2 of the original guideline document?
4. When designing regimens for patients with MDR-TB, is the inclusion of fewer drugs in the regimen (depending on the drug used, the patient's history of its use and isolate susceptibility) more or less likely to lead to the outcomes listed in Table 2 of the original guideline document? *The evidence used to derive recommendations on the duration of treatment was based on an analysis of the same individual patient data collected and described in Question 3 above.*
5. In patients with MDR-TB, is shorter treatment, compared with the duration currently recommended by WHO, more or less likely to lead to the outcomes listed in Table 2 of the original guideline document?
6. In patients with human immunodeficiency virus (HIV) infection and drug-resistant TB receiving antiretroviral therapy, is the use of drugs with overlapping and potentially additive toxicities, compared with their avoidance, more or less likely to lead to the outcomes listed in Table 2 of the original guideline document? *Evidence was reviewed from 10 studies to assess patient treatment outcomes when antiretroviral therapy (ART) and second-line anti-tuberculosis drugs were used together.*
7. Among patients with MDR-TB, is ambulatory therapy, compared with inpatient treatment, more or less likely to lead to the outcomes listed in Table 2 of the original guideline document?

For the scope of question 1, the discussion leading to the recommendations the term rapid tests to those providing a diagnosis within two days of specimen testing, thereby including only tests using molecular techniques (line probe assay and Xpert MDR/RIF). The different groups of drugs referred to in the text are composed of the agents shown in Table 3 of the original guideline document. In the analyses of data for questions 3–5, streptomycin was found to be used but it is generally considered a first-line drug. Later-generation fluoroquinolones included levofloxacin (750mg/day or more), moxifloxacin, gatifloxacin and sparfloxacin. Ciprofloxacin, ofloxacin and levofloxacin (up to 600mg/day) were considered earlier-generation fluoroquinolones for this analysis.

Assessment of Evidence and Its Grading

The evidence review teams assessed the evidence for the questions and their outcomes through a series of systematic literature reviews following an approved methodology that was documented (see Annex 1 of the original guideline document [see the "Availability of Companion Documents" field]).

Modelling work was done in the context of questions 1 and 2. The question on models of care (question 7) was addressed by a review of published and unpublished studies containing a full economic evaluation of patients on MDR-TB treatment.

Where possible, relative effects (hazard ratios, relative risks or odds ratios of an event) were calculated from pooled data of included studies. In two of the analyses, outcome was expressed as the cost per disability-adjusted life year (DALY) averted. The DALY is a summary indicator that expresses the burden of mortality and morbidity into a single value: perfect health is valued at 1 and death at 0 (a year with TB disease is valued at 0.729). For the modelling of rapid drug-susceptibility testing (DST), estimated cost outcomes included total costs for each DST strategy, cost per MDR-TB case prevented, cost per TB-related death avoided and cost per DALY averted. Transmission of resistant strains and subsequent secondary cases were not estimated. For the analysis of models of care (question 7), costs considered for inclusion could be from any of the following perspectives: cost from the health service provider's perspective, cost from the patient's perspective (including direct medical costs as well as indirect costs related to transportation) and total societal cost. Whenever possible, the following outcomes were included in the outcome: proportion of treatment success, default or long-term deaths (including secondary, default and relapse cases) and case reproduction rate (transmission from primary cases).

Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profiles based on the results of the systematic reviews were prepared for each question using a standard approach. These summaries present the effect of the intervention on each outcome (for example, the number of patients with MDR-TB), as well as the quality of the evidence for each outcome. The quality of evidence was assessed using the following criteria: study design, limitations in the studies (risk of bias), imprecision, inconsistency, indirectness, publication bias, magnitude of effect, dose–effect relations and residual confounding. Quality of evidence was categorized into four levels (see the "Rating Scheme for the Strength of the Evidence" field.)

Methods Used to Formulate the Recommendations

Description of Methods Used to Formulate the Recommendations

The first two editions of these guidelines were published in 2006 and 2008 as a collaborative effort of many partners, most of whom were members of the Green Light Committee. This 2011 update follows World Health Organization (WHO) requirements for developing guidelines as specified in the Handbook for Guideline Development (2010), which involve an initial scoping exercise, use of systematic reviews to summarize evidence and application of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to develop recommendations.

The updated guidelines focus on the detection and treatment of drug-resistant tuberculosis (TB) in settings where resources are limited. Priority topics identified by WHO in this field and by its external experts were:

- Case-finding (use of rapid molecular tests; investigation of contacts and other high-risk groups)
- Regimens for multidrug resistant TB (MDR-TB) and their duration in human immunodeficiency virus (HIV)-positive and HIV-negative patients
- Monitoring during treatment
- Models of care

The guidelines are limited to topics not covered by other WHO policy documents published recently, including treatment of drug-susceptible TB and use of antiretroviral agents, treatment of patients with isoniazid-resistant TB and TB infection control. The 2011 update was produced through a systematic process starting in early 2009. Priority areas to be included in the update had been identified from those listed as outstanding areas for future direction following publication of the emergency update (2008). The previous programmatic management of drug-resistant tuberculosis (PMDT) guidelines were evaluated via a user questionnaire. Various experts, including TB practitioners, public health professionals, national TB control programme staff, guideline methodologists, members of civil society and nongovernmental organizations providing technical support, and WHO staff, were invited to form a Guideline Development Group to inform the update process. A second group, comprising national TB control programme staff, WHO regional TB advisors, and clinical and public health experts, was appointed to serve as an External Review Group.

The Guideline Development Group provided input on the selection of questions to address outstanding topics of controversy or areas where changes in policy or practice were warranted. It also selected and scored outcomes to determine those that were critical or important for making decisions on recommendations and to identify the data which were to be sought during retrieval and synthesis of evidence. By September 2009, the scope of the guidelines had been agreed, the questions formulated, and the selection and scoring of the main outcomes had been completed. Between October 2009 and May 2010, teams from leading academic centres were commissioned to review and compile the evidence. The early results of the reviews were made available to members of the Guideline Development Group before and during a meeting to develop the recommendations held at WHO headquarters in Geneva, Switzerland, on 25–27 October 2010.

The Guideline Development Group held teleconferences to discuss the available evidence, the presentation of the results and their impact on making recommendations. One discussant was chosen from among the group's members to assess the evidence for each of the questions and to complement the presentation of the evidence by the evidence review teams. A preparatory meeting was held in September 2010 to review the interim results of the work relating to the questions on treatment regimens and duration, and use of rapid drug susceptibility testing (DST). The group met at WHO headquarters in Geneva, Switzerland, between 25 and 27 October to develop the revised recommendations. A week before the meeting, members were able to review the evidence profiles for each question via a password-protected electronic website (EZ Collab site). During the meeting and in the following months, additional files and successive versions of the guidelines were shared with the group on the same site.

At the meeting, the GRADE evidence profiles were assessed by the members of the Guideline Development Group when preparing the recommendations. The group used standard decision tables to move from evidence to recommendations. One table was prepared for each recommendation to record decisions and ensure that the group uniformly considered the quality of the evidence, the certainty about the balance of benefits versus harms, the similarity in values and the costs of an intervention compared with the alternative. The profiles allowed members to base their judgments when making recommendations on evidence summarized in a concise and uniform manner. Agreement on the recommendations was reached following discussions. In their deliberations, members of the group assessed the level of evidence and judged the strength of the recommendations according to the criteria shown in the "Rating Scheme for the Strength of the Recommendations" field (see web Annex 2 [see the "Availability of Companion Documents" field] for a glossary of GRADE terms).

Apart from the quality of evidence, the strength of a recommendation was determined by the balance between desirable and undesirable effects, values and preferences, and costs or resource allocation. The higher the quality of evidence, the more likely that it leads to a strong

recommendation. However, a strong recommendation may be made in the presence of very low quality evidence given variability in values and preferences between the experts, the balance between desirable and undesirable consequences of an intervention, and resource implications. For instance, evidence from observational studies without randomization is always of low quality, but if the studies are methodologically sound (not downgraded for concerns about the validity) and the estimates of effect are consistent, a strong recommendation may still be possible. It is important to note that when making a conditional recommendation, the group considered its application only to a specific group, population or setting, or that new evidence might change the balance of risk to benefit or that the benefits might not warrant the cost or resource requirements in all settings (see also Table 6 in the original guideline document).

This guideline was developed in compliance with the process for evidence gathering, assessment and formulation of recommendations, as outlined in the WHO Handbook for Guideline Development (version March 2010; available at www.who.int/hiv/topics/mtct/grc_handbook_mar2010_1.pdf; see also the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Assessment of the Strength of the Recommendation

Strength	Definition
Strong	The Guideline Development Group is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Conditional	The Guideline Development Group concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects.

Cost Analysis

For the modelling of rapid drug-susceptibility testing (DST), estimated cost outcomes included total costs for each DST strategy, cost per multidrug-resistant tuberculosis (MDR-TB) case prevented, cost per TB-related death avoided and cost per disability-adjusted life year (DALY) averted. Transmission of resistant strains and subsequent secondary cases were not estimated. For the analysis of models of care, costs considered for inclusion could be from any of the following perspectives: cost from the health service provider's perspective, cost from the patient's perspective (including direct medical costs as well as indirect costs related to transportation) and total societal cost.

- The modelling work showed that rapid testing of both isoniazid and rifampicin at the time of diagnosis was the most cost effective testing strategy for any patient group or setting, even at very low levels of resistance among TB patients (MDR-TB in >1% and isoniazid resistance (other than MDR-TB) in >2%). For previously untreated patients, DST at the start of treatment was a better strategy than waiting to test only those patients who remained sputum-smear positive later in the course of their first-line treatment.
- Cost for sputum smear testing alone ranged between one-fourth to a half of the combined cost of culture and smear testing (based on information from nine studies reviewed for these guidelines). It is likely that this difference may be higher where culture diagnosis is not readily available. More laboratory resources (staff, equipment, utilities) are required to perform culture, and fewer culture laboratories exist in the low-resource conditions of most high-burden countries. In settings where the risk of failure is low, selected patients can be prioritized for monthly culture.
- Cost varied widely across the modelled settings for models of care. The cost per DALY averted by an ambulatory model in one setting was sometimes higher than the cost per DALY averted by a hospitalization model in another setting. However, cost per DALY averted was lower under outpatient-based care than under inpatient-based care in the vast majority (at least 90%) of settings for which cost-effectiveness was modelled. The variation in cost-effectiveness among settings correlated most strongly with the variation in the cost of general health-care services and other non-drug costs. Despite the limitations in the data available, there was no evidence that was in conflict with the recommendation and which indicated that treatment in a hospital-based model of care leads to a more favourable treatment outcome.

Refer to Annex 1 of the original guideline document (see the "Availability of Companion Documents" field) for detailed discussions of these cost analyses.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

The External Review Group commented on the questions during their formulation (in mid-2009) and on a draft text of the guidelines, including recommendations, following comments from the Guideline Development Group (in early 2011). For the initial discussion, eight of the peer reviewers submitted comments that were used for the revised set of priority questions submitted to the evidence review centres for the systematic reviews. Six reviewers made comments on the draft guidelines in early 2011.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

The evidence used to address the questions on which drugs to include (with or without information on their drug susceptibility testing [DST] patterns) and the number of drugs to be used in regimens for multidrug-resistant tuberculosis (MDR-TB) patients was based on studies published in three major systematic reviews. All three reviews searched EMBASE and MEDLINE databases as well as the Cochrane Library and the ISI Web of Science. Studies published before 1970 and those including only extensively drug-resistant tuberculosis (XDR-TB) cases were excluded. The reviewers then pooled individual patient data from studies which had featured in the systematic reviews for a meta-analysis.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate management of drug-resistant tuberculosis
- The likely benefits of rapid drug sensibility testing include increased cure rates, decreased mortality, reduced development of additional drug resistance, and a reduced likelihood of failure and relapse.

Refer to the "Benefits" sections of the original guideline document for a more detailed discussion of potential benefits of each of the recommendations.

Potential Harms

- The harms of rapid drug susceptibility testing (DST) include false-positive results leading to wasted resources, and increased toxicity to the patient from unnecessary administration of second-line medications.
- The risk of additional acquisition of resistance is a concern in cases of unrecognized resistance to some of the drugs used.
- Drug interactions between anti-human immunodeficiency virus therapy and anti-tuberculosis therapy may lead to adverse events. See also Annex 3 of the original guideline document for potentially overlapping toxicities of antiretrovirals and anti-tuberculosis agents.
- There may be some important barriers to accessing clinic-based ambulatory care, including distance to travel and other costs to individual patients.

Refer to the "Risks" sections of the original guideline document for a more detailed discussion of potential harms of each recommendation.

Qualifying Statements

Qualifying Statements

- The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on

the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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Implementation of the Guideline

Description of Implementation Strategy

Publication, Implementation, Evaluation

- The guidelines will be published in English on the World Health Organization (WHO) web site as well as in a peer-reviewed publication. WHO's Stop Tuberculosis (TB) Department will work closely with regional and country offices, the Stop TB Partnership and other implementing partners to ensure their wide dissemination through electronic and paper format.
- A companion manual is planned for 2011 to provide practical information on implementing programmatic management of drug-resistant TB. The manual will update previous guidance on this subject.
- An evaluation of how users have implemented the guidelines will be developed to measure different dimensions of uptake of the recommendations, including the time until adaptation (if any) and barriers to effective implementation.

Implementation Tools

Audit Criteria/Indicators

Foreign Language Translations

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva (Switzerland): World Health Organization; 2011. 44 p. [52 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2008 (revised 2011)

Guideline Developer(s)

World Health Organization - International Agency

Source(s) of Funding

United States Agency for International Development (USAID)

Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The Declaration of Interest forms were completed by all non-World Health Organization (WHO) members of the Guideline Development Group and the External Review Group, as well as the members of the academic centres who were involved in the reviews. Four members of the Guideline Development Group declared interests that were judged to represent a potential conflict and were excused from the sessions of the meeting on 25–27 October 2010 during which recommendations relating to the drug regimens were discussed. Jaime Bayona was a consultant for the development of clinical trial design for studies of an anti-tuberculosis drug manufactured by Otsuka Pharmaceutical Co Ltd (OPC-67683). Charles L. Daley was chairperson of drug safety monitoring for two trials conducted by Otsuka Pharmaceutical Co Ltd. Carole D. Mitnick served as a member of the Scientific Advisory Board of Otsuka Pharmaceutical Co Ltd and had an advisory role on drug OPC-67683. Ma. Imelda Quelapio received support (monetary and nonmonetary) for research from Otsuka Pharmaceutical Co Ltd.

The following members of the academic centres who performed the reviews of evidence from which the recommendations contained in these guidelines are derived presented their findings at the meeting: Matthew Arentz, Melissa Bauer, Richard Menzies, Carole D. Mitnick, Olivia Oxlade, Patricia Pavlinac and Judd L. Walson. They did not participate in the formulation of recommendations related to the respective reviews of evidence that they performed.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization (WHO); 2008. 247 p.

It is expected that the World Health Organization's Stop Tuberculosis (TB) Department, in collaboration with its partners, will review and update these guidelines about four years after their publication or earlier if new evidence, regimens or diagnostic tests become available.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the World Health Organization Web site .

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

Availability of Companion Documents

The following are available:

- Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization (WHO); 2014. 462 p. Electronic copies: Available from the World Health Organization (WHO) Web site .
- Multidrug-resistant tuberculosis (MDR-TB) indicators: A minimum set of indicators for the programmatic management of MDR-TB national tuberculosis control programmes. Geneva, Switzerland: World Health Organization (WHO); 2010, 9 p. Electronic copies: Available in Chinese, English, French, Russian and Spanish translations from the WHO Web site.
- Management of MDR-TB: A field guide. Geneva, Switzerland: World Health Organization (WHO); 2009, 62 p. Electronic copies: Available from the WHO Web site .
- WHO handbook for guideline development. Geneva, Switzerland: World Health Organization (WHO); 2010, 67 p. Electronic copies: Available from the WHO Web site .

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

The original guideline document contains an executive summary and additional information is available in the guideline Annexes 1-3.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 26, 2009. The information was verified by the guideline developer on December 11, 2009. This NGC summary was updated by ECRI Institute on January 2, 2011. This summary was updated by ECRI Institute on October 25, 2013 following the U.S. Food and Drug Administration advisory on Fluoroquinolone Antibacterial Drugs. This summary was updated by ECRI Institute on May 18, 2016 following the U.S. Food and Drug Administration advisory on Fluoroquinolone Antibacterial Drugs.

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